

Inventors: Osborne and Ramesh  
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28. (Amended) A method of treating diabetes or forestalling a clinical symptom indicative of diabetes comprising implanting into an individual cells coexpressing an insulin precursor containing an insulin precursor cleavage site, a glucose-regulated protease capable of cleaving said insulin precursor cleavage site to produce insulin, and a hexosamine biosynthetic pathway enzyme.

#### REMARKS

Claims 1-40 are pending and claims 17-39 are currently under examination in the above identified application. By the present communication claims 17 and 28 have been amended. Support for the amendments to claims 17 and 28 can be found in the specification including, for example, on page 16, line 9, through page 17, line 32 and page 37, line 5, through page 41, line 24. Accordingly, the amendments do not introduce new matter and entry thereof is respectfully requested. A marked-up version of the amended claims to show changes made is attached hereto as Appendix A.

Applicants appreciate the time and helpful comments of Examiner Ewoldt in a personal interview held with Applicants' representative and Dr. Osborne on August 15, 2002. In the interview, the rejections of the claims under 35 U.S.C. § 112, first paragraph were discussed. Applicants believe that the amendments and remarks herein address the considerations discussed during the interview.

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**Rejections Under 35 U.S.C. § 112, First Paragraph**

Claims 17-39, stand rejected under 35 U.S.C. § 112, first paragraph, for lacking enablement of transfected  $\beta$  cells allegedly because such cells would be immediately attacked and killed.

Applicants respectfully submit that the claims recite the term "implanting," which is defined on page 14, lines 6-11, of the specification to mean that the introduced cells "remain viable after implantation and maintain their glucose-regulated insulin secretion for at least one stimulation of glucose uptake." Because Applicants are claiming only viable cells, it is axiomatic that insulin production for at least one stimulation of glucose uptake will result is at least the forestalling of a clinical symptom. Therefore, the claims are fully enabled for the full scope of the invention as claimed.

Furthermore, Applicants have not argued unclaimed limitations with respect to the teachings in the specification for administering immunosuppressive agents or the masking of surface molecules. The rejection at issue is enablement. The law is clear on this point, to enable the claimed invention, all that is required is to teach those skilled in the art how to make and use the invention as claimed without undue experimentation. *Genentech, Inc. v. Novo Nordisk A/S*, 108 F.3d 1361, 1365 (Fed. Cir. 1997), *Johns Hopkins Univ. v. CellPro, Inc.*, 152 F.3d 1342, 1360-61 (Fed. Cir. 1998). Applicants have satisfied this standard.

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Applicants claim implanting cells into an individual where such cells remain viable after implantation for at least one stimulation of glucose uptake. The application teaches various methods for implanting cells of the invention into an individual such that they remain viable for at least one stimulation. Two of such methods for implanting include the use of immunosuppressive agents or masking agents. Applicants' remarks therefore are directed to enablement because they demonstrate that the application teaches methods of implanting such that the introduced cells remain viable. The application's teaching of such methods fall within the scope of the claims. To require Applicants to claim such elements would be unduly limiting and would defeat the purpose of the enablement requirement.

Applicants maintain that the term proinsulin as it is used in the claims and defined in the specification is consistent with the normal usage of the term in the art. As Applicants have previously demonstrated, the prefix "pro" when used in reference to a polypeptide denotes that the polypeptide is a precursor to the mature protein. Accordingly, proinsulin is a precursor of insulin as Applicants define and claim. The definition of proinsulin on page 16, line 9 through page 17, line 12, in the application expressly includes insulin precursor configurations other than that consisting of A, B and C chains (see, for example, page 16, lines 29-32).

However, even if the term differs from its normal usage, the law is clear that it is not improper for the inventor

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to use a term differently than its ordinary meaning. The Federal Circuit has reaffirmed this principle in its decisions in *Markman* and *Vitronics*. In *Markman* the court stated:

For claim construction purposes, the description may act as a sort of dictionary, which explains the invention and may define terms used in the claims. As we have often stated, a patentee is free to be his own lexicographer. The caveat is that any special definition given to a word must be clearly defined in the specification.

*Markman v. Westview Instr.*, 52 F.3d 967, 979-80 (Fed. Cir. 1995) (in banc), *aff'd*, 517 U.S. 370 (1996) (citations omitted) (emphasis added).

The principle that terms can be defined differently than their ordinary meaning was again clearly reaffirmed in *Vitronics* when the court stated:

Although words in a claim are generally given their ordinary and customary meaning, a patentee may choose to be his own lexicographer and use terms in a manner other than their ordinary meaning, as long as the special definition of the term is clearly stated in the patent specification or file history.

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*Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996) (*citing Hoechst Celanese Corp. v. BP Chems. Ltd.*, 78 F.3d 1575, 1578 (Fed.Cir.1996)).

To further prosecution of this application, the claims have been amended to replace the term proinsulin with the term insulin precursor. As defined in the application on, for example, page 16, lines 9-10, the two terms are coextensive in meaning. Accordingly, Applicants maintain that the use of insulin precursor as taught and defined in the application is fully enabled.

Applicant maintains that use of a glucose-regulated protease capable of cleaving the insulin precursor cleavage site of an insulin precursor to produce insulin in the claimed methods is sufficiently enabled by the specification. As set forth previously of record, the specification teaches that insulin can be produced from an insulin precursor having naturally occurring cleavage sites or from an insulin precursor having cleavage sites modified to a cognate recognition site for a desired protease. Several proteases and their cognate recognition sites are taught in the specification or well known in the art. Such teachings are found, for example, on pages 17, lines 13-32, and on page 37, line 23 through page 38, line 10. In view of the teaching and guidance provided in the specification those skilled in the art would have been able to readily modify insulin to include a modified protease site using routine methods. Furthermore, coexpression of the modified insulin with the cognate protease as claimed and taught in the specification would have resulted in

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cleavage of the modified insulin precursor to produce insulin as claimed.

The assertion that furin is the single protease enabled that functions in the method of the claimed invention ignores the definition of proinsulin, or the newly amended term insulin precursor, as well as the teachings and guidance in the specification. For example, the asserted lack of enablement for the use of other proteases such as a PC2 enzyme in conjunction with its cognate cleavage site in the claimed insulin precursor is contrary to the express teachings of the application. As described, for example, on page 17, lines 13-32, the amended term insulin precursor cleavage site includes protease cleavage sites that are derived from molecules other than proinsulin.

It is not the Examiner's prerogative to selectively read the definition of a term clearly provided in the application. *Markman* 52 F.3d 967 at 979-80; *Vitronics* 90 F.3d 1576 at 1582. Accordingly, and again in contrast to the assertion in the Office Action, Applicants' remarks are directed to a claimed limitation because the application sufficiently teaches the use of proteases and cognate cleavage sites other than those that act on naturally occurring proinsulin. Such guidance and teachings have been previously made of record and are summarized below for the Examiner's convenience.

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As set forth above and previously made of record, the application teaches:

- (1) that an insulin precursor region can be amino acid sequences "not normally found in vertebrate proinsulin molecules," (page 16, lines 29-32);
- (2) that the terms "proinsulin cleavage site" or "insulin precursor cleavage site" includes protease cleavage sites that are "not derived from a wild type insulin sequence," (page 17, lines 20-22), and
- (3) the use of proteases and cognate cleavage sites other than those found in naturally occurring proinsulin for cleavage of an insulin precursor into insulin (page 38, lines 1-4, and lines 21-28, for example).

Further, there is no art or evidence of record other than mere assertion that the teachings in the application for mixing and matching proteases and cognate cleavage sites would require undue experimentation. As Applicants have pointed out in, for example, their response dated February 2, 2002, the specificity of PC2 protease described in Smeekins et al. for the C-peptide-A-chain junction is well within the teachings of the application because the application teaches the use of non-wild type insulin cleavage sites together with their cognate protease in a variety of recombinant designs. It would be routine and well known to those skilled in the art to incorporate a PC2 cleavage site at one or more insulin precursor cleavage points to effect the specific cleavage of a claimed insulin precursor when expressed with a glucose-regulated PC2 protease. Accordingly, the art of record supports the teachings of the application.

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In further corroboration, Applicants submit as Exhibit A a declaration under 37 C.F.R. §1.132 where Dr. Robert Ferrell avers that it would be routine for one skilled in the art to incorporate a wide variety of protease cleavage sites into an insulin precursor of the invention for coexpression with a cognate protease that recognizes and cleaves the cleavage site for the production of mature insulin.

Such teachings and guidance within the application as well as corroborating extrinsic evidence shows that the application sufficiently enables those skilled in the art to practice the invention with proteases and cognate cleavage sites other than those specific for a naturally occurring proinsulin form consisting of A, B, and C chains. Accordingly, the application sufficiently enables the full scope of the invention as claimed.

Claims 28-30 and 32-39, stand rejected under 35 U.S.C. § 112, first paragraph, for lacking written description of any hexosamine biosynthetic pathway enzymes other than glutamine:fructose-6-phosphate amidotransferase (GFA) allegedly because the description of the enzymatic product is insufficient to describe the enzyme responsible for the formulation of the product.

To meet the written description requirement the language of the specification must describe the claimed invention so that one skilled in the art can recognize what is claimed. *Enzo Biochem, Inc., v. Gen-Probe Inc.*, 296 F.3d 1316, 1328 (Fed.

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Cir. 2002). Applicants have met this well established standard. The application describes with sufficient clarity numerous species of the claimed invention such that one skilled in the art can recognize the full scope of the invention as claimed. Such description demonstrates not only that Applicants contemplated the invention, but also shows that Applicants were in possession of the claimed invention at the time of filing. *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64 (Fed. Cir. 1991).

The Office Action appears to rely on an alleged lack of explicit support for each and every enzyme within the hexosamine biosynthetic pathway in support of the rejection. However, there is no controlling authority that has departed from the standard that express support for the claimed invention is not a prerequisite for satisfying the written description requirement. In this regard, the *Vas-Cath* court emphasized:

A fairly uniform standard for determining compliance with the "written description" requirement has been maintained throughout: "Although [the applicant] does not have to describe exactly the subject matter claimed, ... the description must clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed.

*Id.* at 1563 (quoting *In re Gosteli*, 872 F.2d 1008, 1012, (Fed.Cir.1989) (citations omitted). Applying this standard, *Vas-Cath* held that, under proper circumstances, drawings alone may provide adequate written description of an invention as required by §112. The court pointed out that elements found in

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Applicant's claims need not correspond exactly to those disclosed in the parent application. Recently, the *Enzo* court has held that reference to a public deposit of a nucleotide sequence when it is not otherwise available in written form constitutes adequate written description. *Enzo*, 296 F.3d at 1325.

The above standard has been applied well before the decision in *Vas-Cath* by the predecessor Court of Customs and Patent Appeals and has been maintained up to the most recent decisions of the Federal Circuit. The court *In re Reynolds* described the principle of inherent written description as follows:

By disclosing in a patent application a device that inherently performs a function or has a property, operates according to a theory or has an advantage, a patent application necessarily discloses that function, theory or advantage, even though it says nothing concerning it. The application may later be amended to recite the function, theory or advantage without introducing prohibited new matter.

*In re Reynolds*, 443 F.2d 384 (C.C.P.A. 1971); accord *In re Smythe*, 480 F.2d 1376 (C.C.P.A. 1973). The sufficiency of inherent written description was affirmed even more plainly when the Court of Customs and Patent Appeals stated "[t]o comply with written description, it is not necessary that the application describe the claimed invention in *ipsis verbis*." *Application of Edwards*, 568 F.2d 1349, 1351-52 (C.C.P.A. 1978). Furthermore, the Federal Circuit has very recently reaffirmed that "the

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disclosure as originally filed does not have to provide in *haec verba* support for the claimed subject matter at issue." *Crown Operations Int'l, Ltd. v. Solutia Inc.*, 289 F.3d 1367, 1376, (Fed.Cir. 2002). This well established standard of not requiring express written description for a claimed invention was yet again reaffirmed by the Federal Circuit's statement that "[i]dentity of description is not necessary." *New Railhead Mfg. L.L.C. v. Vermeer Mfg. Co.*, 298 F.3d 1290, 1296 (Fed. Cir. 2002).

Applicants maintain that the specification provides express support sufficient to satisfy the written description requirement for the invention as claimed. Nevertheless, assuming *arguendo*, that express support was not provided for every claim element, "[t]he burden . . . rests on the PTO in the first instance , and it is up to the PTO to give reasons why a description not in *ipsis verbis* is insufficient." *Application of Edwards*, 568 F.2d at 1354. Applicants respectfully submit that the Office has failed to provide reasons sufficient to meet that burden allocated to it by the Federal Courts.

In this regard, the Office Action sets forth an apparent *pro forma* rejection based entirely on Applicants' alleged lack of express written description for species of a claimed element. To support the rejection, the Examiner chooses an individual claim term and alleges lack of *ipsis verbis* support for its constituent species in the specification. As set forth above, in view of the controlling and established federal case law, lack of identity of description is not synonymous with a lack of written description. In other words, the inquiry into

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whether sufficient written description is provided by the specification cannot properly be based solely on a formulaic approach with no attempt recognize the teachings and guidance of specific embodiments within the specification or the application as a whole. As a result, the Office has not met its burden as to why a description that is not in *ipsis verbis* is insufficient.

In contrast, Applicants have provided specific description of the claimed invention and have further provided adequate teachings and guidance sufficient for one skilled in the art to recognize the invention as claimed. Briefly, the specification describes the intermediates of the hexosamine biosynthetic pathway in the context of a well known pathway. As set forth previously, the specification identifies fructose-6-phosphate, glucosamine-6-phosphate, glucosamine, N-acetyl glucosamine-6-phosphate, N-acetyl glucosamine-1-phosphate and UDP-N-acetyl glucosamine in the context of the hexosamine biosynthetic pathway (see, for example, page 19, lines 5-13 and page 21, lines 10-18). The relationship of these intermediates to each other in the hexosamine biosynthetic pathway was well known in the art as demonstrated, for example, by Figure 1 of McClain et al., *Diabetes* 45:1003-1009 (1996), attached hereto as Exhibit B. More specifically, Figure 1 of McClain et al. shows the series of reactions in the hexosamine biosynthetic pathway including conversion of fructose-6-phosphate to glucosamine-6-phosphate, conversion of glucosamine-6-phosphate to N-acetyl glucosamine-6-phosphate, conversion of N-acetyl glucosamine-6-phosphate to N-acetyl glucosamine-1-phosphate, and conversion of N-acetyl glucosamine-1-phosphate to UDP-N-acetyl glucosamine.

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Furthermore, those skilled in the art would have known or been able to identify a hexosamine biosynthetic pathway enzyme capable of the above-identified hexosamine biosynthetic pathway reactions. In particular, SWISS-PROT entry P43577, attached herewith as Exhibit C, indicates that glucosamine-phosphate N-acetyl transferase (EC 2.3.1.4) was known to convert glucosamine-6-phosphate to N-acetyl glucosamine-6-phosphate (see page 2, under the headings "catalytic activity" and "pathway"). Moreover, as described on page 1 of Exhibit C, the sequence of the protein was entered in SWISS-PROT in November 1995 and was, therefore, known prior to the time of filing. As demonstrated by SWISS-PROT entry P38628, attached herewith as Exhibit D, Phosphoacetylglucosamine mutase (EC 5.4.2.3) was known to convert N-acetyl glucosamine-6-phosphate to N-acetyl glucosamine-1-phosphate and the sequence was entered in SWISS-PROT in October 1995, prior to the time of filing. The enzyme UDP-N-acetyl glucosamine pyrophosphorylase (EC 2.7.7.23) was known to convert N-acetyl glucosamine-1-phosphate to UDP-N-acetyl glucosamine and its sequence was known prior to the time of filing, as shown in SWISS-PROT entry P43123, attached herewith as Exhibit E. Because those skilled in the art would have known of or been able to identify enzymes capable of performing the reactions of the hexosamine biosynthetic pathway described in the specification, they would have understood that applicants were in possession of the hexosamine biosynthetic enzymes recited in the claims. Accordingly, reconsideration and withdrawal of this rejection is respectfully requested

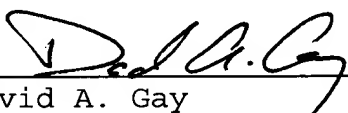
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CONCLUSION

In light of the amendments and remarks herein, Applicants submit that the claims are now in condition for allowance and respectfully request a notice to this effect. The Examiner is invited to call the undersigned agent if there are any questions.

Respectfully submitted,

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#### APPENDIX A

A marked up version of the amended claims to show changes made is provided below. Text to be added is underlined and text to be deleted is in brackets.

17. (Amended) A method of treating diabetes or forestalling a clinical symptom indicative of diabetes comprising implanting into an individual cells coexpressing an insulin precursor [proinsulin] containing an insulin precursor [a proinsulin] cleavage site and a glucose-regulated protease capable of cleaving said an insulin precursor [proinsulin] cleavage site to produce insulin.

28. (Amended) A method of treating diabetes or forestalling a clinical symptom indicative of diabetes comprising implanting into an individual cells coexpressing an insulin precursor [proinsulin] containing an insulin precursor [a proinsulin] cleavage site, a glucose-regulated protease capable of cleaving said an insulin precursor [proinsulin] cleavage site to produce insulin, and a hexosamine biosynthetic pathway enzyme.